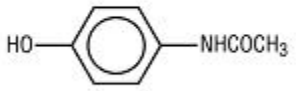
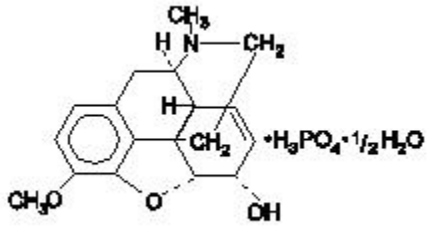
ACETAMINOPHEN AND CODEINE PHOSPHATE - acetaminophen and codeine phosphate tablet
Ranbaxy Pharmaceuticals Inc.

DESCRIPTION

Each tablet contains:
#3 Codeine Phosphate USP . . . . . 30 mg
Acetaminophen USP . . . . . .….300 mg
or
#4 Codeine Phosphate USP . . . . . 60 mg
Acetaminophen USP . . . .…. 300 mg
Inactive ingredients are magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium lauryl sulfate, and sodium starch glycolate.
Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



$C_8H_9NO_2$ M.W. 151.16
Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation.
Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro-4,5α-epoxy-3- methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \bullet 1/2H_2O$ M.W. 406.37

CLINICAL PHARMACOLOGY

Acetaminophen and codeine phosphate tablets USP combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.
Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine.
Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.
Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS AND USAGE

Acetaminophen and codeine phosphate tablets USP are indicated for the relief of mild to moderately severe pain.

CONTRAINDICATIONS

Acetaminophen and codeine phosphate tablets USP should not be administered to patients who have previously exhibited hypersensitivity to any component.

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of this product or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Patients: This drug should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Ultra-rapid Metabolizers of Codeine

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regiments, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African, Americans, and 16 to 28% in North Africans, Ethiopians and Arabs. Data is not available for other ethnic groups.

When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and should inform their patients about these risks and the signs of morphine overdose. (See **PRECAUTIONS-Nursing mothers**)

Information for Patients

Codeine may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Codeine may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Caution patients that some people have a variation in a liver enzyme and change codeine into morphine more rapidly and completely than other people. These people are ultra-rapid metabolizers and more likely to have higher-than-normal levels of morphine in their blood after taking codeine which can result in overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. In most cases, it is unknown if someone is an ultra-rapid codeine metabolizer.

Nursing mothers taking codeine can also have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Instruct nursing mothers to watch for signs of morphine toxicity in their infants including increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's doctor immediately if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911(or local emergency services).

Drug Interactions

Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with codeine may produce paralytic ileus.

Carcinogenesis and Mutagenesis and Impairment of Fertility

No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy

Teratogenic Effects

Pregnancy category C

Codeine

A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase

in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no studies in humans, and the significance of these findings to humans, if any, is not known.

Acetaminophen and codeine phosphate tablets USP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery
Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated.
If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see **OVERDOSAGE**). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers
Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. Because of the potential for serious adverse reactions in nursing infants from acetaminophen, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.
Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.
The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in Africans, Americans and 16 to 28% in the North Africans, Ethiopians and Arabs. Data is not available for other ethnic groups.
The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing. Prescribers should closely monitor mother infant pairs and notify treating pediatricians about the use of codeine during breastfeeding. (See **PRECAUTION – General**- *Ultra-rapid Metabolizers of Codeine*).

ADVERSE REACTIONS
The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain and pruritus.
At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE
Acetaminophen and codeine phosphate tablets USP are a Schedule III controlled substance.
Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic containing medications.

OVERDOSAGE

Acetaminophen
Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.
The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

Codeine
Signs and Symptoms: Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.
Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.
An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.
Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION
Dosage should be adjusted according to severity of pain and response of the patient.
It should be kept in mind, however, that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects.
Equivalently high doses in children would have similar effects.
The usual adult dosage for tablets is:

	Single Doses (Range)	Maximum 24 Hour Dose
Codeine Phosphate	15 mg - 60 mg	360 mg
Acetaminophen	300 mg - 1000 mg	4000 mg

Doses may be repeated up to every 4 hours.
The prescriber must determine the number of tablets per dose, and the maximum number of tablets per 24 hours, based upon the above dosage guidance. This information should be conveyed in the prescription.
For children, the dose of codeine phosphate is 0.5 mg/kg.

HOW SUPPLIED
Acetaminophen and codeine phosphate tablets USP 300 mg/30 mg are white, round, tablets, debossed "RX" over "562" on one side and "3" on the other side. Each tablet contains 300 mg of acetaminophen USP and 30 mg of codeine phosphate USP. They are supplied as follows:
Bottles of 100 (NDC 63304-562-01)
Bottles of 500 (NDC 63304-562-05)
Bottles of 1000 (NDC 63304-562-10)
Acetaminophen and codeine phosphate tablets USP 300 mg/60 mg are white, round, tablets, debossed "RX" over "561" on one side and "4" on the other side. Each tablet contains 300 mg of acetaminophen USP and 60 mg of codeine phosphate USP. They are supplied as follows:
Bottles of 100 (NDC 63304-561- 01)
Bottles of 500 (NDC 63304-561-05)
Store at 20 - 25° C (68 - 77° F). (See USP Controlled Room Temperature). Protect from light. Do not refrigerate. Do not freeze.

Dispense in tight, light-resistant container as defined in the USP.
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: CorePharma LLC
Middlesex, NJ 08846 USA
November 2007